



Current Data on Cardiovascular and Gastrointestinal Lesions in Novel Covid-19 Coronavirus Infection

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Abstract: The purpose of presenting this review is to present the current evidence on cardiovascular and gastrointestinal lesions in novel coronavirus infection (COVID-19). The review focuses on summarising the global data known by June 2020. An attempt is made to provide a pathophysiological rationale for the structural and functional changes of internal organs. The article focuses on the lesions of the cardiovascular system, liver and small intestine, as well as the issues of diagnosis and rationalisation of basic therapy of inflammatory bowel disease, arterial hypertension and ischaemic heart disease.

Key words: COVID-19, liver and small intestine damage, cardiovascular disorders, treatment strategies.

Introduction: A coronavirus outbreak in China's Hubei Province in late December 2019 led to the World Health Organisation declaring a pandemic on 11 March 2020. By the end of May, there were already more than 6 million ill people worldwide and nearly 400,000 deaths from COVID-19. The world was faced with an unknown infection causing predominantly severe lower respiratory tract damage requiring oxygen support and artificial ventilation. The virus has also challenged the scientific community: clinicians are in urgent need of understanding the basic characteristics of the virus, the mechanisms of infection and disease progression, and the emergence of potentially effective drugs and a reliable vaccine suitable for mass prophylaxis. At the same time, there is a lack of objective information: publications on these issues, which appear on a daily basis in considerable volume, are often contradictory, mostly describing clinical cases and the results of prospective and retrospective clinical observations. At the same time, a large number of randomised trials have been initiated, which will provide convincing answers to the existing questions, especially with regard to patient management [1].

Regularly updated versions of the temporary guidelines "Prevention, Diagnosis and Treatment of Emerging Coronavirus Infection (COVID-19)" contain a detailed description of COVID-19 diagnostic methods, modern approaches to differentiated treatment, and highlight the issues of prevention and compliance with sanitary and epidemiological regime. The section on clinical manifestations of COVID-19 focuses on clinical symptoms characteristic of lung damage, which in most cases determines the prognosis of the disease [2]. Meanwhile, COVID-19 can also affect other organs and systems of the body, including cardiovascular and digestive organs. Mortality statistics are also affected by fatal changes caused by the virus and activation of chronic pre-existing heart and

gastrointestinal diseases. This review focuses on summarising the global evidence known by June 2020 regarding issues of pathophysiology, diagnosis and rationalisation of basic therapy for inflammatory bowel disease, arterial hypertension and ischaemic heart disease.

COVID-19 and gastrointestinal pathology

To date, it has been established that the receptor for angiotensin-converting enzyme type 2 (ACE-2) is expressed in large quantities not only in type 2 alveolar cells, but also in cholangiocytes, cardiomyocytes, epithelial cells of proximal renal tubules and bladder, oesophagus, and gastrointestinal epithelium. Moreover, enterocytes occupy the leading position here. As for transmembrane serine protease type 2 (TMPRSS2), its production is equally expressed both in enterocytes and colonicocytes [3, 4]. Viral nucleocapsid was detected in mucosal biopsy specimens of the gastric, duodenal and rectal mucosa, which confirms the possibility of infection of the digestive tube [3]. Moreover, viral RNA continues to be detected in stool samples long after negative results in nasopharyngeal contents, raising some controversy about a possible faecal-oral transmission mechanism [5, 6, 7]. The current position of a number of researchers is that there is no risk of infection through the patient's faeces, which is quite consistent with the available data on other coronavirus syndromes (SARS and MERS), and the identification of viral RNA in stools is explained by the transit time (shortened during diarrhoea, presence of concomitant pathology of the small and large intestine).

Moreover, a virus-inactivating effect of colonocyte secretion has been established, which significantly reduces the viral load and "contagiousness" of faeces [3, 8]. It should be noted that low pH reduces virus activity within 10 minutes, and bile components acting as detergents (lecithin, sodium salt of taurocholic acid), contrary to expectations, have no inhibitory effect on it. The question of increased permeability of the intestinal wall as a potential risk factor for dissemination of the virus with the development of systemic damage, including lungs and liver, especially in those cases when the disease debuts with gastrointestinal manifestations, remains open. Computed tomography of the abdominal cavity organs in 31% of hospitalised patients with moderate to severe PCOS revealed changes in the relief of the intestinal wall; in resuscitation patients, signs of microthrombosis with the development of intestinal wall ischaemia were detected in 2.7% of cases. At ultrasound examination of the liver and biliary tract, signs of cholestasis were registered in 51% of cases [9]. On the other hand, American researchers observed that in the presence of gastrointestinal complaints, the probability of a positive test for JUSO increased to 70%, with GI involvement associated with a more prolonged but less severe course of infection [10]. However, there are, however, opposite observations [11, 12]. Patients with inflammatory bowel disease (IBD) receiving baseline immunosuppressive therapy deserve special attention in terms of infection risk. It should be noted that the presence of IBD, as well as the use of genetically engineered biologic drugs (vedulizumab, in patients with inflammatory bowel disease) (vedulizumab, ustekinumab), does not change the expression of genes encoding ACE-2 production. [3]. There is an opinion that patients with ICD, constantly receiving pathogenetic therapy, have a risk of infection similar to the population, and the probability of development of "cytokine storm" in them can be reduced [13]. The experience of Italian researchers, based on the data of the international registry 8ESIJA-SHP, indicates the need to continue treatment with TNF-alpha inhibitors and interleukin-6 blockers. Moreover, according to the data of this registry it was found that the number of severe and moderately severe cases was significantly lower in patients with CLC treated with anti-TNF-alpha therapy than in patients treated with glucocorticosteroids (GCS): only 15% required hospitalisation, less than 3% died against 67% and 25%, respectively, in patients treated with GCS [14]. Patients receiving azathioprine, methotrexate, 6-mercapto-purine and high (more than 20 mg/day) doses of GCS require an individual approach: the decision is usually made in favour of their withdrawal [12]. The approach to endoscopic procedures and surgeries in the context of the COVID-19 pandemic should also be reviewed. Diagnostic manipulations and surgical treatment are considered

possible only after mandatory testing for COVID-19 RNA. The issues of triage, hospitalisation in the "clean" zone, postponement of planned interventions, and allocation of risk groups for the necessity of emergency esophagogastroduodenoscopy, colonoscopy, and laparoscopy are elaborated and regularly updated in the relevant international documents [11, 15]. Liver damage, in addition to instrumentally detectable cholestasis, is also manifested by a moderate elevation of liver enzymes (AST, ALT, LDH) in about one third of hospitalised patients with COVID-19. It may result from immune damage caused by an inflammatory response. The degree of elevation tends to correlate with the severity of viral infection. Cases of acute liver failure have been described if a "cytokine storm" develops and severe hypoxia occurs. In mild course of infection, laboratory changes are transient and do not require correction [16, 17]. A viral cytopathic effect cannot be excluded at this stage either. Convincing data in favour of this hypothesis have not been obtained so far, according to the data of single postmortem studies in China, as well as earlier in MERS and SARS virions were not identified in hepatic tissue [16, 17]. Histological changes in COVID-19 were represented by hepatocyte dystrophy, microvascular steatosis, focal necrosis with neutrophilic infiltration, as well as increased numbers of lymphocytes and monocytes in portal margins and microthrombosis of sinusoid capillaries [17].

In addition, laboratory findings are often associated with the administration of antiviral drugs (lopinavir/ritonavir), also indicating potential drug-induced liver damage [16]. This may explain the variability in laboratory changes in patients from different clinics receiving a variety of drug combinations, including those with paracetamol, oseltamivir, and umifenovir. It is worth noting that alkaline phosphatase and gamma-GTP, a marker of cholangiocyte damage, were rarely elevated, despite the presence of ACE2 receptors in these cells. In this regard, patients with primary sclerosing cholangitis and biliary cirrhosis deserve a separate dynamic study to evaluate the effect of COVID-19 on prognosis. Data on the association of existing liver disease with the course of SARSCoV-2 infection are currently very limited, and many questions remain open. This is partly due to the lack of anamnestic data on chronic liver disease in COVID-19 patients in descriptive Chinese studies. For example, chronic viral hepatitis B (more common in China than in Europe) does not appear to influence COVID-19 outcomes [12]. One study reported a significant increase in the concentration of monocyte chemotaxis factor (MCP-1) in patients with viral infection, which is known to play a key role in the progression of non-alcoholic fatty liver disease [18].

Thus, COVID-19 virus can affect the gastrointestinal tract in several ways: its receptor-mediated entry into cells is possible; in addition, it can induce inflammation and alter the permeability of mucous membranes; immune inflammation can activate chronic liver disease, whose damage can be exacerbated by the use of unregulated drugs. . Data on the association of existing liver disease with the course of SARSCoV-2 infection are currently very limited, and many questions remain open. This is partly due to the lack of anamnestic data on chronic liver disease in COVID-19 patients in descriptive Chinese studies. For example, chronic viral hepatitis B (more common in China than in Europe) does not appear to influence COVID-19 outcomes [12]. One study reported a significant increase in the concentration of monocyte chemotaxis factor (MCP-1) in patients with viral infection, which is known to play a key role in the progression of non-alcoholic fatty liver disease [18].

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COVID-19 and cardiovascular pathology

Cardiovascular damage can generally be viewed from a similar perspective: there is a risk of viral myocarditis, immune myocardial damage, activation of pre-existing chronic diseases, primarily coronary heart disease (CHD) and arterial hypertension (AH), as well as the intrinsic cardiotoxic

effects of antiviral drugs, or alteration of the pharmacokinetics and expected effects of baseline drugs, including antiaggregants and anticoagulants.

Cardiovascular pathology can be diagnosed in 40% of patients who die from JUSH-19 infection and acts as an independent prognostic risk factor for death [19, 20].

ACE-2 signalling pathways involved in the cardiac damage cascade, dysregulation of the renin-angiotensin-aldosterone system (RAAS), and the possibility of using ACE inhibitors and sartans in COVID-19 have become the subject of a wide discussion and required the release of a number of consensus documents clarifying the positions of the world's leading cardiology societies on this issue [1, 20]. Although there is consensus on the continuation of RAAS blockers in pandemic settings, as well as the other classes of antihypertensive drugs, long-term follow-up of these patients is required. The number of "hypertensives", as well as their adherence to therapy and achievement of target BP values, differs between countries and has not been considered to influence prognosis in viral infection to date. It is possible that age, ethnicity, polymorphism of genes encoding ACE-2, number of comorbidities including diabetes mellitus rather than drug therapy recommended in these cases have a greater prognostic impact. There is also an opinion that aeropollutants (nitrogen and sulphur dioxide, carbon monoxide) also negatively affect the course of viral infection. Single experimental studies leave more questions: for example, in the work of German researchers, it was found that cardiomyocytes and pericytes express ACE-2, while fibroblasts, endothelial cells and leukocytes express it to a much lesser extent. Expression varies according to nosology: in aortic stenosis it is greater than in heart failure with reduced ejection fraction. ACE inhibitors have a greater effect on increasing ACE-2 expression than sartans. In contrast, another group of European cardiologists, based on peripheral blood ACE-2 levels, found no difference between those taking ACE inhibitors and those taking sartans, while significantly higher serum ACE-2 concentrations were noted in men than in women. The protective role of ACE-2 with respect to the development of a complicated course of COVID-19 is also debated: its high level may be a useful reservoir in the context of increased viral particle binding [19]. Taking into account this fact, a clinical trial on the use of recombinant human ACE-2 for the treatment of patients with COVID-19 has been initiated. Continuation of statins in the setting of coronavirus infection is certainly favourable. Moreover, given their known pleiotropic effects (primarily anti-inflammatory and antioxidant), they may potentially be beneficial during the course of the disease. There is evidence of their favourable effects on the lipid profile in patients receiving antiretroviral therapy and in rheumatoid arthritis patients treated with tocilizumab. Starting with low doses and regular monitoring of liver enzymes and creatine kinase will avoid adverse events during COVID-19 treatment [2, 8].

A prospective 12-year follow-up of patients with SARS allows to state the development of various forms of carbohydrate metabolism disorders (in 60%), hyperlipidaemia (in 68%), cardiovascular disorders (in 44%) [9]. It is possible that the new virus, due to its similarity to the previous virus, may cause similar changes, which should be taken into account when implementing preventive measures, including the use of statins. The frequent immediate cardiac complications of SARS were hypotension, myocarditis, arrhythmias and sudden cardiac death (SCD). MERS was also accompanied by myocarditis and heart failure. Due to a certain closeness of the coronaviruses, myocarditis also develops in patients with COVID-19, a few days after the onset of fever. However, pericarditis remains an uncharacteristic symptom. The mechanisms of SARS-CoV-2-induced myocardial damage may be related to ACE-2 activation, hypoxia due to respiratory failure, and activation of autoimmune-type adaptive mechanisms through molecular mimicry [19]. It was found that elevated troponin I levels induced by cardiac lesions were associated with significantly higher mortality in COVID-19, especially in ICU patients. Moreover, this circumstance necessitated the introduction of certain norms in the assessment of highly specific troponin T/I levels for differential diagnosis between acute cardiac

damage (myocarditis, Takotsubo syndrome, myocardial infarction type) and exacerbation of pre-existing diseases, or COVID-associated elevation of cardioselective markers. Autopsy data revealed mononuclear infiltration in the areas of cardiomyocyte necrosis, to a lesser extent CD4+ T cells, which does not contradict the Dalas criteria for myocarditis. Virions were detected only in tissue macrophages in the interstitium, which may be associated with their migration from lung tissue or with transient viremia. To date, it remains unclear whether this infiltration occurs as part of a systemic inflammatory response or in response to viral invasion, and there is no consensus on the effect of virus-associated myocarditis on left ventricular ejection fraction. According to some data, acute heart failure due to infectious myocardial damage may occur in 23% of patients, and the detection of signs of new cardiomyopathy - in 33%. This fact, as well as possible right ventricular overload in respiratory distress syndrome, requires attention when calculating water load and infusion therapy [3, 10]. Overall, it is noteworthy that there is no consensus on the optimal treatment regimen for presumed COVID-19-associated myocarditis, especially in its fulminant course, and the search for possible effective techniques and drugs continues. As part of this search, data on the efficacy of transgenic cells (cardiosphere cells) secreting exosomes with pro- and anti-inflammatory properties were obtained in experiments on laboratory animals.

The results of the experiment initiated the clinical trial "CdcS for Cytokine Storm in Covid Syndrome Trial" with the recruitment of patients in critical condition with lymphopenia and "cytokine storm". The issues of correlation of viral infection with the development of acute coronary syndrome (ACS), routing and determination of revascularisation strategy are covered in detail in the guidelines of leading cardiology associations [1, 20]. The diagnosis of ACS is difficult, taking into account the similarity of clinical picture: myocardial infarction (MI), according to some data, can be the first symptom of a new coronavirus infection in 85.7% of cases, in one third of patients angiography does not reveal occlusion. It is believed that the rationale for the occurrence of type 2 IM is microvascular thrombosis on the background of virus-induced endothelial dysfunction and thrombophilia. Management of such patients on the background of COVID-19 is an example of difficult choice of optimal combination of drugs taking into account antiviral therapy and its influence on pharmacokinetics, in particular, antiaggregants. Thus, in COVID-19 in patients with ACS for a year ticagrelor may be the drug of choice in the absence of contraindications to it due to a significantly lower incidence of sepsis and pulmonary infections with no effect on spirometry parameters in comparison with clopidogrel. However, it should be taken into account that its concentration increases in the presence of lopinavir/ritonavir [2]. The number of sudden deaths during the quarantine period in March-April 2020, especially in the home, was also strongly correlated with the increase in the number of infected patients. Arrhythmic deaths as well as the development of non-fatal rhythm disturbances may be associated with the direct damaging effect of the virus on the cardiac conducting system, worsening of the course of chronic cardiac pathology, electrolyte imbalance, hyperactivity of the sympathoadrenal system and the development of acute ischaemia.

Antimalarial drugs, with which there were high hopes as antiviral agents, also contributed to the development of arrhythmias before they were excluded from the protocols. Another apparently underestimated proarrhythmic risk factor should be considered the influence of inflammatory cytokines (interleukin-1, -6 and tumour necrosis factor- α) on the electrophysiological characteristics of the conducting system, which can modulate the work of potassium and calcium channels in cardiomyocytes with prolongation of the QT interval on the ECG and development of rhythm disturbances such as torsades de pointes [19]. Technologies for providing remote counselling support to patients with cardiovascular diseases deserve special discussion. Thanks to them, it has been possible not only to reduce the risk of infection of elderly patients during face-to-face contact, but also to significantly reduce costs. First of all, telemedicine projects using applications for smartphones and other gadgets have proved themselves [4]. In addition, a European COVID-19

registry and data collection on the impact of the new coronavirus infection on the cardiovascular system, the course of cardiovascular diseases and traditional methods of their treatment have been initiated [5].

Conclusions: In summary, the COVID-19 pandemic has triggered a veritable boom of research worthy of dozens of reviews and monographs, most of which certainly shed light on the mechanisms of interaction between the new virus and the human body. However, many questions of pathogenesis still remain unsolved. We have an idea of the clinical picture, identify predictors of an unfavourable course of the disease, but we have not yet created a single clear algorithm of pathogenetic therapy, often using auxiliary and symptomatic drugs and aids. New effective therapeutic strategies will definitely emerge in the near future. And even if COVID-19 becomes a ghostly memory, the lessons learnt during this troubled time will undoubtedly serve to benefit the treatment of other severe hyperimmune diseases with cardiovascular, respiratory and digestive system involvement.

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